REMARKS

Claims 1-6 were previously withdrawn; the applicant acknowledges the Examiner's removal of an earlier restriction requirement in response to the applicant's statement that "CIP" and "CIP fragment" are not patentably distinct claim limitations in this context. As a result, Claims 1-6 are reinstated and are now designated either as "original" or "currently amended" in the above claim listing. Claims 10-16 were canceled earlier. Consequently, claims 1-9 and 17-25 are now under consideration. All claims stand rejected.

Claim 1 has been rephrased for clarity and to remove a parenthetical expression objected to by the Examiner. It also expressly specifies, as one of ordinary skill would have understood from the original claim, that the epitope recognized by the antibody in CIP is "inaccessible for binding" in CAP. The claim scope has not been changed, and no new matter is added.

Claim 3 was likewise amended for clarity: the meaning has not been changed from that which would have been understood by one of ordinary skill in the art, so no new matter is added.

Claim 4 was amended by the removal of the phrase "protein binding surface" from the list of supports for the bound antibody, because the Examiner deemed that phrase indefinite. No new matter is added.

Claim 5 was amended to depend from claim 1 rather than claim 3. This is necessary for the method of claim 5 to operate as described, because the final complex could not precipitate from solution if one of the antibodies were bound to a solid support as required by claim 3. It was also amended to recite that the second antibody binds to a portion of CIP other than that to which the first antibody binds. This is supported by the specification at page 7, second paragraph. Thus the amendments add no new matter.

Claim 6 was amended to remove the phrase "or signal generating component", since one of skill in the art would understand 'label' to encompass all of the detection-enabling components

recited. It is also amended to present each such label in the singular so that the Markush group language conforms to standard practice. No new matter is added by these amendments.

Claim 7 was amended like claim 1. In addition, the initial complex was identified as a "first complex", and the final complex as a "second complex". This clarifies that the labeled antibody can be either the first or the second, as is clear from the specification at page 7, second paragraph (noting that the order of binding of the two antibodies can be reversed). Thus the amendment better describes the claimed process, but adds no new matter.

Claim 7 was also amended to include a limitation requiring that the amount of antibody or antibody fragment must be "sufficient to bind the CIP present". This is supported by the specification at page 7, paragraph 2, which describes the multi-antibody process and says that the first antibody must be used "in an amount sufficient to bind the CIP present." Thus the amendment adds no new matter.

Claim 8 is amended to correspond to claim 7, where the term 'second complex' is used rather than 'labeled complex', since the label may be introduced by either the first or the second antibody. The amendment only deleted the word 'labeled', thus it adds no new matter.

Claim 17 is amended in the same way claims 1 and 7 were, to remove the parenthetical expression "(PTH_{1-84})". The preamble is also amended for clarity. No new matter is added.

Claim 19 was amended by the removal of the phrase "protein binding surface" from the list of supports for the bound antibody, because the Examiner deemed that phrase indefinite. No new matter is added.

Claim 20 was amended to depend from claim 7 rather than claim 19, because the final complex would not 'precipitate' from solution if either of the antibodies were bound to a solid surface. No new matter is added.

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In addition to the amendments explained above, in several places the word 'said' when used as a definite article has been replaced with the word 'the' for consistency. The amendments are supported by the application as filed and add no new matter; the applicant requests that the Examiner enter the amended claims.

Rejections under 35 U.S.C. § 112, first paragraph: Written Description.

Claims 1-9 and 17-25 stand rejected under the first paragraph of 35 U.S.C. § 112, for an alleged failure to comply with the written description requirement. The Examiner points out that the claims require the use of an antibody with defined selectivity, and asserts that "there is no description of an antibody in the specification that distinguishes a peptide sequence for CIP that presents an epitope on CIP and does not bind to CAP."

The applicant respectfully traverses this rejection. In Enzo Biochem. V. Gen-Probe, Inc., 323 F.3d 956, 964 (Fed. Cir. 2002), the Federal Circuit cited the PTO Guidelines for the written description requirement when it stated:

> For example, the PTO would find compliance with 112 paragraph 1, for a claim to an isolated antibody capable of binding to an antigen X, notwithstanding the functional definition of the antibody, in light of the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature. Id. The court adopted the USPTO Guidelines as persuasive authority for the proposition that a claim directed to "any antibody which is capable of binding to antigen X" would have sufficient support in a written description that disclosed "fully characterized antigens."

In Noelle v. Lederman, the court relied on this quotation from *Enzo* when it stated that an applicant can claim an antibody by its binding affinity, "as long as an applicant has disclosed a '*fully characterized* antigen,' either by its structure, formula, chemical name, or physical properties..." 69 USPQ2d 1508, 1513-14 (Fed. Cir. 2004) (emphasis in original). In *Noelle*, which is based on an interference initiated in 1999, the senior party only disclosed an accession number for

a hybridoma that produced the mouse antibody, which did not describe the human antigen or antibody, thus the human antibody was not adequately described in that case. Nevertheless, the court reinforced the statements from *Enzo* saying that disclosure of the antigen by structure would suffice to describe an antibody.

Here, the applicant has described the antigen of interest, CIP, by structure. The present version of the claims defines CIP as follows: "the CIP comprises a contiguous portion of PTH, the PTH having an amino acid sequence set forth in SEQ ID NO:3, and the CIP having an N-terminal amino acid residue starting at position 7 of the PTH and a C-terminal amino acid residue ending at position 84 of the PTH." Thus the antigen of interest is defined precisely by its amino acid sequence, which effectively provides both a structure and a formula. The Examiner notes that the descriptive language used in the specification is "prophetic in nature and does not indicate that such a distinguishing antibody has been produced at the time of filing." Respectfully, the applicant points out that prophetic language is fully permissible; indeed, in the Guidelines on Written Description, an example in which an antibody is described by its antigen alone is deemed to satisfy the written description requirement, with no indication that such an antibody had been produced. Synopsis of Application of Written Description Guidelines, http://www.uspto.gov/web/menu/written.pdf at pg 59-60.

The claimed antibody is described by reference to its antigen, CIP, which is structurally described. The chief difference between the example in the USPTO guidelines and the present situation is the addition of an additional selection criterion here, which requires that the antibody not cross-react with CAP (PTH), which is also precisely defined by structure. That added limitation, however, adds only a routine screening requirement to the process for selecting the appropriate antibody, and the specification at page 9 describes this screening process. Since the screening would be a routine step and is described in the specification, it is not "undue" experimentation under the *Wands* standards (In re Wands, 8 USPQ2d at 1404); furthermore, the Federal Circuit said "antibody technology is well developed and mature" at least as early as 2002, supporting the applicant's assertion that such screening is routine. See the *Enzo* quote above.

Antibody technology was highly developed and predictable at the time the application was filed, the antigen of interest is "fully characterized" since it is described by structure, and only routine experimentation (screening) would be required to select an antibody that meets all of the limitations of the claim. The applicant thus asserts that the specification satisfies the written description requirement with respect to the antibody required to practice the invention, and requests withdrawal of this rejection.

Rejections under 35 U.S.C. § 112, first paragraph: Enablement.

The Examiner further asserts that the specification does not enable one of ordinary skill to practice the invention without undue experimentation, because the requisite antibody is not described or well known in the art. Because the antibody is not well known, the Examiner alleges that "one of ordinary skill in the art would have a low level of predictability in the art."

The applicant respectfully traverses this rejection. As explained above, antibody technology is "well developed and mature" according to the Federal Circuit; indeed, it is well developed with respect to human parathyroid hormone and fragments thereof. The specification summarizes several references that utilize various antibody detection methods for hPTH, focused mainly on giving an accurate measurement of intact hPTH present in a sample that also contains fragments of hPTH, since such fragments skew the result if they cross-react with the antibody that binds hPTH. For example, Gao, et al., discloses a dual antibody method that selectively binds hPTH(1-34) and hPTH (1-84) yet does not cross react with hPTH (4-16), (28-48), (39-84), (66-84), or hPTH-rP (1-86)—the last of which is a related peptide that is two residues longer than hPTH (1-84). Clinica Chimica Acta, 245, pg. 39-59 (1996) (this reference was considered by the Examiner in the first office action, mailed 21 October 2003). The specification also mentions an example of an antibody that binds selectively to CAP but not to CIP.

Gao, et al., demonstrates that it was within the skill in the art to produce antibodies that selectively bind to one peptide comprising hPTH or a fragment thereof while distinguishing other closely related peptides. Most interesting for our purposes is the Gao antibody that does not bind to

hPTH-rp (1-86) (a 'related peptide' having two additional amino acids), yet recognizes the shorter peptide hPTH (1-84). This is analogous to the selectivity pattern required of an antibody useful for the presently claimed invention. Such an antibody must not bind to CAP, which is hPTH (1-84), but it must bind to CIP, which is a shorter version of CAP.

Another example of an antibody specifically binding a truncated form of PTH and not binding to the full-length peptide is described by D'Amour, et al., Clinical Chemistry 49:12, pg. 2037-44 (2003) **[Exhibit A]**. D'Amour discloses a second form of PTH (1-84) that was not previously recognized. The new form of PTH (1-84) is recognized by antibodies that bind to the N-terminal region of PTH (1-84) (The peak at fractions 42-43 shown in the CA-PTH assay in Figure 1 on page 2039). This new form of PTH (1-84) is not recognized by an antibody against the 15-20 region of PTH, which is the antibody used in the T-PTH assay (*See* the T-PTH assay in Figure 1 on page 2039). These results are further explained on pages 2040 (left column) and 2041-2043. The antibody used in the T-PTH assay binds to an epitope at PTH (15-20). The T-PTH assay detects PTH (7-84), but does not detect or barely detects the newly discovered form of PTH (1-84). Therefore, this result demonstrates that an antibody that binds to an epitope of a shorter PTH peptide may not bind to a longer PTH peptide in which the same epitope is inaccessible for binding with the same antibody.

It was known in the art before this application was filed that it was possible to discriminate between closely related peptides, even in this same family of peptides, with an antibody. Antibodies that specifically bind to PTH peptides at the N-terminal, C-terminal and sequences in between were well known. It was also known that peptide antigens can comprise non-contiguous amino acids, and that the three-dimensional structure of a protein can bring distal groups together to form an antigen. Rao, KVS, Antigens, Encyclopedia of Life Sciences, 1-7, Nature Publishing Group (2001) (available online at http://www.fhcrc.org/labs/stoddard/MCB_spring_core/nature02240.pdf) **[Exhibit B—see Figure 1]**. Furthermore, it is known that it is possible to produce an antibody that binds one peptide in the PTH family and does not bind to a longer analog of that peptide. And obviously the addition of more

residues to the N-terminus of a peptide could render an epitope on the peptide inaccessible by folding over that epitope.

The present claims are drawn to an antibody capable of binding specifically to CIP (PTH (7-84)) without binding to PTH (1-84). Production of antibodies that bind PTH (7-84) was clearly a routine matter when the application was filed, and antibody technology was described by the court as "well developed and mature". Since it was also known that differential binding analogous to that required for the claimed antibody could be achieved, the systematic screening methods described in the specification would enable one of ordinary skill to select an appropriate antibody with which to practice the claimed invention. While some experimentation would be required in order to select one of the PTH (7-84) antibodies that does not bind to PTH (1-84), it would not be "undue" in light of (1) the state of the prior art as summarized above, (2) the predictability of the art of antibody production as demonstrated by the above references, (3) the relative skill in this "well developed and mature" art as recognized by the courts, (4) the guidance given in the specification for screening methods to find an antibody with the necessary selectivity, and (5) the narrow scope of the claims, which focus on distinguishing two specific single peptides. See Wands which requires a balancing of such factors. Thus this basis for rejection of the claims can properly be withdrawn, and the applicant requests reconsideration and withdrawal of the rejection.

Rejections under 35 U.S.C. § 112, second paragraph: Indefiniteness.

The Examiner alleges that claim 1 is indefinite, because it fails to expressly set forth a step for the separation of the bound and unbound forms of the labeled antibody. Without such a separation, the Examiner asserts that "one would obtain a positive signal whether or not binding had occurred."

The applicant believes that it is well within the ordinary skill in the art to recognize the need to separate bound from unbound labeled antibody prior to analyzing the sample in certain antibody assays; in other such well-known assays, though, binding of antibody to antigen can be

detected without a need for physical separation. The specification refers to attaching the antibody "to a colloidal particle or moiety that can be used to detect a signal change" and then measuring "the change in signal due to the formation of the complex." Thus physical separation of bound and unbound antibody is necessary where detection is based on the presence or absence of a radioisotope, for example; but it is not necessary where detection is based on, for example, fluorescence measurements that change upon binding of the antibody to the antigen.

Because antibody binding assays are so commonly used and well understood, the applicant believes it is within the ordinary skill in the art to determine which detection methods to use, and to determine accordingly whether a physical separation of bound antibody complex from unbound antibody is necessary. Consequently, one of ordinary skill would recognize whether a separation step were necessary in a given system. A separation step would be utilized where necessary, and such a step would not be required otherwise. The applicant thus asserts that an additional step for removal of unbound labeled antibody is unnecessary in some cases, and would be understood by one of ordinary skill in the art when it was necessary, and requests that this rejection accordingly be withdrawn.

The Examiner also objects to the use of parenthetical expression "(PTH_{1-84})" in claims 1 and 7; since the parenthetical expressions were only for emphasis, they have been deleted in the present amendment. The term PTH_{1-84} has thus been removed from the claims.

Claims 4 and 19 were rejected as indefinite because the phrase, "protein binding surface" was used. The applicant believes this term is generally understood to encompass any means of adhering or binding a protein to a solid surface, and is perhaps coextensive with 'bound to a solid support' in other claims; therefore, to advance prosecution, that term has been removed by the present amendment.

Claim 7 was deemed 'vague and indefinite' because it is allegedly "unclear how the method will work if the label is on the second antibody." The method of claim 7 involves allowing a first antibody (Ab1) to selectively bind CIP in the presence of any CAP present, and a second

antibody (Ab2) to bind to another portion of CIP, forming a ternary complex. Once Ab1 distinguishes CIP from CAP, Ab2 can provide measurable signal disclosing the localization of the ternary complex. So if Ab1 were bound to a solid support, the signal of Ab2 would be bound to the solid support only to the extent CIP was present in the initial sample to bind to Ab1. If Ab1 were in solution, the binding of Ab2 could cause precipitation, for example, so that its signal could be read in the precipitate to the extent CIP was present in the initial sample.

A claim limitation has been added to claim 7, stating that the amount of the first antibody should be sufficient to bind all CIP present; if that is met, the signal of Ab2 should account for all of the CIP initially present even though Ab2 does not itself distinguish bound from unbound CIP. Thus the applicant believes that the claimed method would be clearly understood by one of ordinary skill, and the applicant requests that this rejection be withdrawn.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw all outstanding rejections of the claims and to pass this application to issue. Nevertheless, the applicant recognizes that the subtleties of language sometimes create unanticipated issues when one attempts to provide a precise verbal description of complex technology. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

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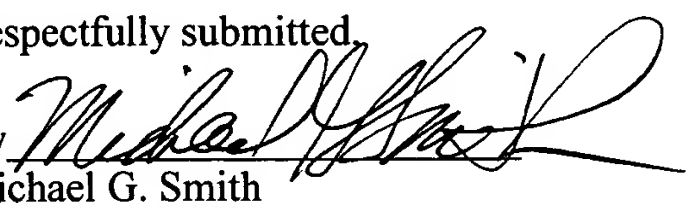
In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no.532212001500. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: December 10, 2004

Respectfully submitted,

By 

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